

CLAIMS:

What is claimed is:

1. A method for inducing intracellular hyperthermia comprising the step of administering
 5 an amount of a mitochondrial uncoupling agent sufficient to induce intracellular hyperthermia.
2. The method of claim 1, wherein the mitochondrial uncoupling agent is 2,4 dinitrophenol.
3. The method of claim 1, wherein the mitochondrial uncoupling agent is selected from the
 10 group consisting of: classic uncouplers, including 2,4 dinitrophenol, clofazimine, albendazole, cambendazole, oxibendazole, triclabendazole (TCZ), 6-chloro-5-[2,3-dichlorophenoxy]-2-methylthio-benzimidazole and their sulfoxide and sulfone metabolites, thiobendazole, rafoxanide, bithionol, niclosamide, eutypine, various lichen acids (hydroxybenzoic acids) such as (+)usnic acid, vulpinic acid and atranorin, 2', 5-dichloro-3-t-butyl-4'-nitrosalicylanilide (S-
 15 13), 3, 4', 5-trichlorosalicylanilide (DCC), platanetin, 2- trifluoromethyl-4, 5, 6, 7-tetrachlorobenzimidazole (TTFB), 1799, AU-1421, 3,4,5,6,9,10-hexahydro-14,16-dihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1,7(8H)-dione (zearalenone), N,N¹-bis-(4-trifluoromethylphenyl)-urea, resorcylic acid lactones and their derivatives, 3,5-di-t-butyl-hydroxybenzylidenemalononitrile(SF6847), 2,2,-bis (hexafluoroacetyl) acetone, triphenyl
 20 boron, carbonylcyanide 4-trifluoromethoxyphenylhydrazine (FCCP), tributylamine (TBA), carbonyl cyanide 3-chlorophenylhydrazine (ClCCP), 1, 3, 6, 8-tetranitrocarbazole, tetrachlorobenzotriazole, 4-iso-octyl-2,6-dinitrophenol(Octyl-DNP), 4-hydroxy-3,5-diidobenzonitrile, mitoguazone (methylglyoxal bisguanylhydrazine), pentachlorophenol (PCP), 5-chloro-2-mercatobenzothiazole (BZT-SH), tribromoimidazole (TBI), N-(3-trifluoromethylphenyl)-anthranilic acid (Flufenamic acid), 4-nitrophenol, 4, 6-dinitrocresol, 4-isobutyl-2,6-dinitrophenol, 2-azido-4-nitrophenol, 5-nitrobenzotriazole, 5-chloro-4-nitrobenzotriazole, tetrachlorobenzotriazole, methyl-o-phenylhydrazine, N-phenylanthranilic acid, N-(3-nitrophenyl)anthranilic acid, N-(2,3-dimethylphenyl) anthranilic acid, mefenamic acid, diflunisal, flufenamix acid, N-(3-chlorophenyl) anthranilic acid, carbonyl cyanide 4-trifluoromethoxyphenylhydrazine (FCCP), SR-4233 (Tirapazamine), atovaquone, carbonyl
 30 cyanide 4-(6'-methyl-2'-benzothiazyl)-phenylhydrazine(BT-CCP), ellipticine, olivacine, ellipticinium, isoellipticine and related isomers, methyl-0-phenylhydrazonocynoaceticacid,methyl-0-(3-chlorophenylhydrazono) cyanoacetic acid, 2-(3'-chlorophenylhydrazono)-3-oxobutyronitrile, thiosalicylic acid, 2-(2',4-dinitrophenylhydrazono)-

3-oxo-4,4-demethylvaleronitrile, relanium, melipramine, and other diverse chemical entities including unsaturated fatty acids (up to C₁₄ optimum), sulflaramid and its metabolite perfluorooctane sulfonamide (DESFA), perfluorooctanoate, clofibrate, Wy-14, 643, ciprofibrate, and fluoroalcohols; ionophorous antibiotic uncouplers, including gramicidin, nigericin, tyrothricin, tyrocidin, valinomycin, alamethicins, harzianin HA V, saturnisporin SA IV, zervamicins, magainin, cecropins, melittin, hypelcins, suzukacillins, monensins, trichotoxins, antiamoebins, crystal violet, cyanine dyes, cadmium ion, trichosporin-B and their derivatives; and other heterogeneous coupling compounds, including desaspidin, ionized calcium (Ca⁺⁺), uncoupling proteins such as UCPI-1, UCP-2, UCP-3, PUMP (Plant Uncoupling Mitochondrial Protein), histones, polylysines, A206668-a protein, and compound K23187.

4. The method of claim 1, wherein the mitochondrial uncoupling agent is a conjugate comprising 2,4 dinitrophenol.

5. The method of claim 1, further wherein the induced intracellular hyperthermia is used in the diagnosis or treatment of infections, malignancies or other medical conditions.

6. The method of claim 5, wherein the induced intracellular hyperthermia is used in the diagnosis or treatment of infections, malignancies or other medical conditions selected from the group consisting of cancer, and infections or infestations.

7. The method of claim 5, wherein the induced intracellular hyperthermia is used in the diagnosis or treatment of cancer.

8. The method of claim 5, wherein an animal is administered the mitochondrial uncoupling agent and a separate medication is administered, wherein the second medication increases the overall metabolic rate of the animal, the metabolic rate of a specific target tissue in the animal, or an increase in free radical flux.

9. The method of claim 8, wherein the second medication is selected from the group consisting of glucagon, arbutamine, dobutamine, vasopressin, glutamine, proline, octanoate, methylene blue (tetramethylthionine), ubiquinone, menadione, hematoporphyrin, polyunsaturated fatty acids including linoleic (double bonds at carbons 9 and 12), alpha-linolenic (double bonds at carbons 9, 12, and 15), gamma-linolenic (double bonds at carbons 6, 9, and 12),

arachidonic (double bonds at carbons 5, 8, 11, and 14), eicosapentaenoic (double bonds at 5, 8, 11, 14, and 17), docosahexenoic (double bonds at carbons 4, 7, 10, 13, 16, and 19), *cis*-parinaric (double bonds at 9, 11, 13, and 15) and, monounsaturated fatty acids including oleic (double bond at carbon 9), erucic (double bond at carbon 13), phenazine methosulfate, 2,6-dichlorophenolindophenol, coenzyme Q1, CoQ2 and their analogs duroquinone and decylubiquinone.

10. The method of claim 5, wherein the induced intracellular hyperthermia involve the induction of heat shock proteins.

11. The method of claim 5, a second therapeutic agent, or therapy, is administered.

12. The method of claim 11, wherein the second, therapeutic agent or therapy, is selected from the group consisting of: anti-fungal agents, including Amphotericin B, Griseofulvin, Fluconazole (Diflucan), Intraconazole, 5 fluoro-cytosine (Flutocytosine, 5-FC), Ketatoconazole and Miconazole; anti-bacterial agents, including beta lactam rings (penicillins), macrocyclic lactone rings (macrolides), polycyclic derivatives of naphacenecarboxamide (tetracyclines), amino sugars in glycosidic linkages (aminoglycosides), peptides (bacitracin, gramicidin, polymyxins, etc.), nitrobenzene derivatives of dichloroacetic acid, large ring compounds with conjugated double bond systems (polyenes), various sulfa drugs including those derived from sulfanilamide (sulfonamides, 5-nitro-2-furanyl compounds (nitrofurans), quinolone carboxylic acids (nalidixic acid), fluorinated quinolones (ciprofloxan, enoxacin, ofloxacin, etc.), nitroimidazoles (metronidazole), peptide antibiotics (such as bacitracin, bleomycin, cactinomycin, capreomycin, colistin, dactinomycin, gramicidin A, enduracitin, amphomycin, gramicidin J, mikamycins, polymyxins, stendomycin, actinomycin; aminoglycosides represented by streptomycin, neomycin, paromycin, gentamycin, ribostamycin, tobramycin, amikacin; lividomycin beta lactams represented by benzylpenicillin, methicillin, oxacillin, hetacillin, piperacillin, amoxicillin and carbenicillin; lincosaminides represented by clindamycin, lincomycin, celesticetin, desalicytin; chloramphenicol; macrolides represented by erythromycins, lankamycin, leucomycin, picromycin), nucleosides (such as 5-azacytidine, puromycin, septacidin and amicitin; phenazines represented by myxin, lomofungin, iodine), oligosaccharides (including curamycin and everninomycin; sulfonamides represented by sulfathiazole, sulfadiazine, sulfanilimide, sulfapyrazine) polyenes (including amphotericins, candicidin and nystatin, polyethers tetracyclines (including doxycyclines, minocyclines, methacyclines,

chlortetracyclines, oxytetracyclines, demeclocyclines), nitrofurans (including nitrofurazone, furazolidone, nitrofurantoin, furium, nitrovin and nifuroxime), and quinolone carboxylic acids (including nalidixic acid, piromidic acid, pipemidic acid and oxolinic acid); antiviral agents including interferons α , β and γ , amantadine, rimantadine, arildone, ribavirin, acyclovir, abacavir, vidarabine (ARA-A) 9- β -D-ribofuranosyl-2-propanoyl methylguanine (DHPG), ganciclovir, enviroxime, foscarnet, amplitgen, podophyllotoxin, 2,3-dideoxythymidine (ddC), iododeoxyuridine (IDU), trifluorothymidine (TFT), dideoxyinosine (ddi), d4T, 3TC, zidovudine, efavirenz, protease inhibitors such as indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, and specific antiviral antibodies; anti-cancer drugs, including cell cycle-specific agents (including structural analogs or antimetabolites of methotrexate, mercaptopurine, fluorouracil, cytarabine, thioguanine, azacitidine), bleomycin peptide antibiotics, such as podophyllin alkaloids including etoposide (VP-16) and teniposide (VM-26), various plant alkaloids such as vincristine, vinblastine, and paclitaxel, anti-neoplastic cell cycle-nonspecific agents such as various alkylating compounds such as busulfan, cyclophosphamide, mechlorethamine, melphalan, altaretamine, ifosfamide, cisplatin, dacarbazine, procarbazine, lomustine, carmustine, lomustine, semustine, chlorambucil, thiotepa and carboplatin; various hormones, hormone agonists and biologic response modifying agents, including flutamide, prednisone, ethinyl estradiol, diethylstilbestrol, hydroxyprogesterone caproate, medroxyprogesterone, megestrolacetate, testosterone, fluoxymesterone and thyroid hormones such as di-, tri- and tetraiodothyroidine, the aromatase inhibitor, amino glutethimide, the peptide hormone inhibitor octreotide and gonadotropin-releasing hormone agonists such as goserilin acetate and leuprolide, biologic response modifiers such as various cytokines, interferon alpha-2a, interferon alpha-2b, interferon-gamma, interferon-beta, interleukin-1, interleukin-2, interleukin-4, interleukin-10, monoclonal antibodies (anti-HER-2/*neu* humanized antibody), tumor necrosis factor, granulocyte-macrophage colony-stimulating factor, macrophage-colony-stimulating factor, various prostaglandins, phenylacetates, retinoic acids, leukotrienes, thromboxanes and other fatty acid derivatives; and radiation therapy.

13. The method of claim 1, wherein the mitochondrial uncoupling agent is an analog of 2,4 dinitrophenol.

14. The method of claim 1, wherein the mitochondrial uncoupling agent is a derivative of 2,4 dinitrophenol.

15. A method for inducing intracellular free radicals comprising the step of administering an amount of a mitochondrial uncoupling agent sufficient to induce intracellular free radicals.

16. The method of claim 15, wherein the mitochondrial uncoupling agent is 2,4
5 dinitrophenol.

17. The method of claim 15, wherein the mitochondrial uncoupling agent is selected from the group consisting of: classic uncouplers, including 2,4 dinitrophenol, clofazimine, albendazole, cambendazole, oxibendazole, triclabendazole (TCZ), 6-chloro-5-[2,3-
10 dichlorophenoxy]-2-methylthio-benzimidazole and their sulfoxide and sulfone metabolites, thiobendazole, rafoxanide, bithionol, niclosamide, eutypine, various lichen acids (hydroxybenzoic acids) such as (+)usnic acid, vulpinic acid and atranorin, 2', 5-dichloro-3-t-butyl-4'-nitrosalicylanilide (S-13), 3, 4', 5-trichlorosalicylanilide (DCC), platanetin, 2-trifluoromethyl-4, 5, 6, 7-tetrachlorobenzimidazole (TTFB), 1799, AU-1421, 3,4,5,6,9,10-
15 hexahydro-14,16-dihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1,7(8H)-dione (zearalenone), N,N¹-bis-(4-trifluoromethylphenyl)-urea, resorcylic acid lactones and their derivatives, 3,5-di-t-butyl-hydroxybenzylidenemalononitrile(SF6847), 2,2,-bis (hexafluoroacetyl) acetone, triphenyl boron, carbonylcyanide 4-trifluoromethoxyphenylhydrazone (FCCP), tributylamine (TBA), carbonyl cyanide 3-
20 chlorophenylhydrazone (CICCP), 1, 3, 6, 8-tetranitrocarbazole, tetrachlorobenzotriazole, 4-isooctyl-2,6-dinitrophenol(Octyl-DNP), 4-hydroxy-3,5-diiodobenzonitrile, mitoguazone (methylglyoxal bisguanylhydrazone), pentachlorophenol (PCP), 5-chloro-2-mercatobenzothiazole (BZT-SH), tribromoimidazole (TBI), N-(3-trifluoromethylphenyl)-anthranilic acid (Flufenamic acid), 4-nitrophenol, 4, 6-dinitrocresol, 4-isobutyl-2,6-
25 dinitrophenol, 2-azido-4-nitrophenol, 5-nitrobenzotriazole, 5-chloro-4-nitrobenzotriazole, tetrachlorobenzotriazole, methyl-o-phenylhydrazone, N-phenylanthranilic acid, N-(3-nitrophenyl)anthranilic acid, N-(2,3-dimethylphenyl) anthranilic acid, mefenamic acid, diflunisal, flufenamix acid, N-(3-chlorophenyl) anthranilic acid, carbonyl cyanide 4-trifluoromethoxyphenylhydrazone (FCCP), SR-4233 (Tirapazamine), atovaquone, carbonyl
30 cyanide 4-(6'-methyl-2'-benzothiazyl)-phenylhydrazone(BT-CCP), ellipticine, olivacine, ellipticinium, isoellipticine and related isomers, methyl-0-phenylhydrazonocynoacetic acid, methyl-0-(3-chlorophenylhydrazono) cyanoacetic acid, 2-(3'-chlorophenylhydrazono)-3-oxobutyronitrile, thiosalicylic acid, 2-(2',4-dinitrophenylhydrazono)-3-oxo-4,4-demethylvaleronitrile, relanium, melipramine, and other diverse chemical entities

including unsaturated fatty acids (up to C₁₄ optimum), sulflaramid and its metabolite perfluorooctane sulfonamide (DESFA), perfluorooctanoate, clofibrate, Wy-14, 643, ciprofibrate, and fluoroalcohols; ionophorous antibiotic uncouplers, including gramicidin, nigericin, tyrothricin, tyrocidin, valinomycin, alamethicins, harzianin HA V, saturnisporin SA IV, zervamicins, magainin, cecropins, melittin, hypelcins, suzukacillins, monensins, trichotoxins, antiameobins, crystal violet, cyanine dyes, cadmium ion, trichosporin-B and their derivatives; and other heterogeneous uncoupling compounds, including desaspidin, ionized calcium (Ca⁺⁺), uncoupling proteins such as UCPI-1, UCP-2, UCP-3, PUMP (Plant Uncoupling Mitochondrial Protein), histones, polylysines, A206668-a protein, and compound K23187.

18. The method of claim 15, wherein the mitochondrial uncoupling agent is a conjugate comprising 2,4 dinitrophenol.

19. The method of claim 15, wherein the mitochondrial uncoupling agent is a derivative of 2,4 dinitrophenol.

20. The method of claim 15, wherein the mitochondrial uncoupling agent is a analog of 2,4 dinitrophenol.

21. The method of claim 15, further wherein the induced intracellular free radicals are used in the diagnosis or treatment of infections, malignancies or other medical conditions.

22. The method of claim 13, wherein the induced intracellular free radicals are used in the diagnosis or treatment of infections, malignancies or other medical conditions selected from the group consisting of cancer, and bacterial, parasitic, fungal, and viral infections or infestations.

23. The method of claim 21, wherein an animal is administered the mitochondrial uncoupling agent and a separate medication is administered, wherein the second medication increases the overall metabolic rate of the animal, the metabolic rate of a specific target tissue in the animal, or an increase in free radical flux.

24. The method of claim 23, wherein the second medication is selected from the group consisting of glucagon, arbutamine, dobutamine, vasopressin, glutamine, proline, octanoate, methylene blue (tetramethylthionine), ubiquinone, menadione, hematoporphyrin,

polyunsaturated fatty acids including linoleic (double bonds at carbons 9 and 12), alpha-linolenic (double bonds at carbons 9, 12, and 15), gamma-linolenic (double bonds at carbons 6, 9, and 12), arachidonic (double bonds at carbons 5, 8, 11, and 14), eicosapentaenoic (double bonds at 5, 8, 11, 14, and 17), docosahexenoic (double bonds at carbons 4, 7, 10, 13, 16, and 19), *cis*-parinaric (double bonds at 9, 11, 13, and 15) and, monounsaturated fatty acids including oleic (double bond at carbon 9), erucic (double bond at carbon 13), phenazine methosulfate, 2,6-dichlorophenolindophenol, coenzyme Q1, CoQ2 and their analogs duroquinone and decylubiquinone.

25. The method of claim 21 wherein the intracellular free radicals are used in the diagnosis or treatment of Lyme disease.

26. The method of claim 21, wherein the induced intracellular free radicals involve the induction of heat shock proteins.

27. The method of claim 15, a second, therapeutic agent or therapy is administered.

28. The method of claim 27, wherein the second, therapeutic agent, or therapy, is selected from the group consisting of: anti-fungal agents, including Amphotericin B, Griseofulvin, Fluconazole (Diflucan), Intraconazole, 5 fluoro-cytosine (Flutocytosine, 5-FC), Ketatoconazole and Miconazole; anti-bacterial agents, including beta lactam rings (penicillins), macrocyclic lactone rings (macrolides), polycyclic derivatives of naphacenecarboxamide (tetracyclines), amino sugars in glycosidic linkages (aminoglycosides), peptides (bacitracin, gramicidin, polymyxins, etc.), nitrobenzene derivatives of dichloroacetic acid, large ring compounds with conjugated double bond systems (polyenes), various sulfa drugs including those derived from sulfanilamide (sulfonamides, 5-nitro-2-furanyl compounds (nitrofurans), quinolone carboxylic acids (nalidixic acid), fluorinated quinolones (ciprofloxan, enoxacin, ofloxacin, etc.), nitroimidazoles (metronidazole), peptide antibiotics (such as bacitracin, bleomycin, cactinomycin, capreomycin, colistin, dactinomycin, gramicidin A, enduracitin, amphomycin, gramicidin J, mikamycins, polymyxins, stendomycin, actinomycin; aminoglycosides represented by streptomycin, neomycin, paromycin, gentamycin, ribostamycin, tobramycin, amikacin; lividomycin beta lactams represented by benzylpenicillin, methicillin, oxacillin, hetacillin, piperacillin, amoxicillin and carbenicillin; lincosaminides represented by clindamycin, lincomycin, celesticetin, desalicyetin; chloramphenicol; macrolides represented by erythromycins,

lankamycin, leucomycin, picromycin), nucleosides (such as 5-azacytidine, puromycin, septacidin and amicetin; phenazines represented by myxin, lomofungin, iodine), oligosaccharides (including curamycin and everninomycin; sulfonamides represented by sulfathiazole, sulfadiazine, sulfanilimide, sulfapyrazine) polyenes (including amphotericins, candicidin and nystatin, polyethers tetracyclines (including doxycyclines, minocyclines, methacyclines, chlortetracyclines, oxytetracyclines, demeclocyclines), nitrofurans (including nitrofurazone, furazolidone, nitrofurantoin, furium, nitrovin and nifuroxime), and quinolone carboxylic acids (including nalidixic acid, piromidic acid, pipemidic acid and oxolinic acid); antiviral agents including interferons α , β and γ , amantadine, rimantadine, arildone, ribavirin, acyclovir, abacavir, vidarabine (ARA-A) 9-1,3-dihydroxy-2-propoxy methylguanine (DHPG), ganciclovir, enviroxime, foscarnet, amplitagen, podophyllotoxin, 2,3-dideoxythymidine (ddC), iododeoxyuridine (IDU), trifluorothymidine (TFT), dideoxyinosine (ddi), d4T, 3TC, zidovudine, efavirenz, protease inhibitors such as indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, and specific antiviral antibodies; anti-cancer drugs, including cell cycle-specific agents (including structural analogs or antimetabolites of methotrexate, mercaptopurine, fluorouracil, cytarabine, thioguanine, azacitidine), bleomycin peptide antibiotics, such as podophyllin alkaloids including etoposide (VP-16) and teniposide (VM-26), various plant alkaloids such as vincristine, vinblastine, and paclitaxel, anti-neoplastic cell cycle-nonspecific agents such as various alkylating compounds such as busulfan, cyclophosphamide, mechlorethamine, melphalan, altaretamine, ifosfamide, cisplatin, dacarbazine, procarbazine, lomustine, carmustine, lomustine, semustine, chlorambucil, thiotepa and carboplatin; various hormones, hormone agonists and biologic response modifying agents, including flutamide, prednisone, ethinyl estradiol, diethylstilbestrol, hydroxyprogesterone caproate, medroxyprogesterone, megestrolacetate, testosterone, fluoxymesterone and thyroid hormones such as di-, tri- and tetraiodothyroidine, the aromatase inhibitor, amino glutethimide, the peptide hormone inhibitor octreotide and gonadotropin-releasing hormone agonists such as goserelin acetate and leuprolide, biologic response modifiers such as various cytokines, interferon alpha-2a, interferon alpha-2b, interferon-gamma, interferon-beta, interleukin-1, interleukin-2, interleukin-4, interleukin-10, monoclonal antibodies (anti-HER-2/*neu* humanized antibody), tumor necrosis factor, granulocyte-macrophage colony-stimulating factor, macrophage-colony-stimulating factor, various prostaglandins, phenylacetates, retinoic acids, leukotrienes, thromboxanes and other fatty acid derivatives; and radiation therapy.

29. A method of treating disease in an animal by inducing intracellular hyperthermia comprising the step of administering an amount of a mitochondrial uncoupling agent sufficient to induce intracellular hyperthermia.

5 30. The method of claim 29, wherein the mitochondrial uncoupling agent is 2,4 dinitrophenol.

31. The method of claim 29, wherein the mitochondrial uncoupling agent is a conjugate comprising 2,4 dinitrophenol.

10 32. The method of claim 29, wherein the disease is selected from the group consisting of cancer, and infections or infestations of bacterial, parasitic, fungal, and viral pathogens.

15 33. The method of claim 29, wherein the induced intracellular hyperthermia is used in the treatment of cancer.

20 34. The method of claim 29, wherein an animal is administered the mitochondrial uncoupling agent and a separate medication is administered, wherein the second medication increases the overall metabolic rate of the animal, the metabolic rate of a specific target tissue in the animal, or an increase in free radial flux.

25 35. The method of claim 34, wherein the second medication is selected from the group consisting of glucagon, arbutamine, dobutamine, vasopressin, glutamine, proline, octanoate, methylene blue (tetramethylthionine), ubiquinone, menadione, hematoporphyrin, polyunsaturated fatty acids including linoleic (double bonds at carbons 9 and 12), alpha-linolenic (double bonds at carbons 9, 12, and 15), gamma-linolenic (double bonds at carbons 6, 9, and 12), arachidonic (double bonds at carbons 5, 8, 11, and 14), eicosapentaenoic (double bonds at 5, 8, 11, 14, and 17), docosahexenoic (double bonds at carbons 4, 7, 10, 13, 16, and 19), *cis*-parinaric (double bonds at 9, 11, 13, and 15) and, monounsaturated fatty acids including oleic (double
30 bond at carbon 9), erucic (double bond at carbon 13), phenazine methosulfate, 2,6-dichlorophenolindophenol, coenzyme Q1, CoQ2 and their analogs duroquinone and decylubiquinone.

36. The method of claim 29, wherein the induced intracellular hyperthermia used involves

the induction of heat shock proteins.

37. A method for diagnosing disease in an animal by chemically inducing intracellular hyperthermia comprising the step of administering an amount of a mitochondrial uncoupling agent sufficient to induce intracellular hyperthermia.

38. The method of claim 37, wherein the mitochondrial uncoupling agent is 2,4 dinitrophenol.

39. The method of claim 37, wherein the mitochondrial uncoupling agent is a conjugate comprising 2,4 dinitrophenol.

40. The method of claim 37, wherein the disease is selected from the group consisting of cancer, and infections or infestations of bacterial, parasitic, fungal, and viral pathogens.

41. The method of claim 37, wherein the induced intracellular hyperthermia is used in the diagnosis or treatment of cancer.

42. The method of claim 37, wherein an animal is administered the mitochondrial uncoupling agent and a separate medication is administered, wherein the second medication increases the overall metabolic rate of the animal, the metabolic rate of a specific target tissue in the animal, or an increase in free radical flux.

43. The method of claim 42, wherein the second medication is selected from the group consisting of glucagon, arbutamine, dobutamine, vasopressin, glutamine, proline, octanoate, methylene blue (tetramethylthionine), ubiquinone, menadione, hematoporphyrin, polyunsaturated fatty acids including linoleic (double bonds at carbons 9 and 12), alpha-linolenic (double bonds at carbons 9, 12, and 15), gamma-linolenic (double bonds at carbons 6, 9, and 12), arachidonic (double bonds at carbons 5, 8, 11, and 14), eicosapentaenoic (double bonds at 5, 8, 11, 14, and 17), docosahexaenoic (double bonds at carbons 4, 7, 10, 13, 16, and 19), *cis*-parinaric (double bonds at 9, 11, 13, and 15) and, monounsaturated fatty acids including oleic (double bond at carbon 9), erucic (double bond at carbon 13), phenazine methosulfate, 2,6-dichlorophenolindophenol, coenzyme Q1, CoQ2 and their analogs duroquinone and decylubiquinone

44. The method of claim 37, wherein the induced intracellular hyperthermia involves the induction of heat shock proteins.

5 45. The method of claim 37, wherein the mitochondrial uncoupling agent is selected from the group consisting of: classic uncouplers, including 2,4 dinitrophenol, clofazimine, albendazole, cambendazole, oxibendazole, triclabendazole (TCZ), 6-chloro-5-[2,3-dichlorophenoxy]-2-methylthio-benzimidazole and their sulfoxide and sulfone metabolites, thiobendazole, rafoxanide, bithionol, niclosamide, eutypine, various lichen acids
10 (hydroxybenzoic acids) such as (+)usnic acid, vulpinic acid and atranorin, 2', 5-dichloro-3-t-butyl-4'-nitrosalicylanilide (S-13), 3, 4', 5-trichlorosalicylanilide (DCC), platanetin, 2-trifluoromethyl-4, 5, 6, 7- tetrachlorobenzimidazole (TTFB), 1799, AU-1421, 3,4,5,6,9,10-hexahydro-14,16-dihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1,7(8H)-dione (zearalenone), N,N¹-bis-(4-trifluoromethylphenyl)-urea, resorcylic acid lactones and their
15 derivatives, 3,5-di-t-butyl-hydroxybenzylidenemalononitrile(SF6847), 2,2-bis(hexafluoroacetyl) acetone, triphenyl boron, carbonylcyanide 4-trifluoromethoxyphenylhydrazone (FCCP), tributylamine (TBA), carbonyl cyanide 3-chlorophenylhydrazone (ClCCP), 1, 3, 6, 8-tetranitrocarbazole, tetrachlorobenzotriazole, 4-isooctyl-2,6-dinitrophenol(Octyl-DNP), 4-hydroxy-3,5-diiodobenzonitrile, mitoguazone
20 (methylglyoxal bisguanylhyazone), pentachlorophenol (PCP), 5-chloro-2-mercato benzothiazole (BZT-SH), tribromoimidazole (TBI), N-(3-trifluoromethylphenyl)-anthranilic acid (Flufenamic acid), 4-nitrophenol, 4, 6-dinitrocresol, 4-isobutyl-2,6-dinitrophenol, 2-azido-4-nitrophenol, 5-nitrobenzotriazole, 5-chloro-4-nitrobenzotriazole, tetrachlorobenzotriazole, methyl-o-phenylhydrazone, N-phenylanthranilic acid, N-(3-nitrophenyl)anthranilic acid, N-(2,3-dimethylphenyl) anthranilic acid, mefenamic acid,
25 diflunisal, flufenamix acid, N-(3-chlorophenyl) anthranilic acid, carbonyl cyanide 4-trifluoromethoxyphenylhydrazone (FCCP), SR-4233 (Tirapazamine), atovaquone, carbonyl cyanide 4-(6'-methyl-2'-benzothiazyl)-phenylhydrazone(BT-CCP), ellipticine, olivacine, ellipticinium, isoellipticine and related isomers, methyl-0-
30 phenylhydrazonocynoacetic acid, methyl-0-(3-chlorophenylhydrazono) cyanoacetic acid, 2-(3'-chlorophenylhydrazono)-3-oxobutyronitrile, thiosalicylic acid, 2-(2',4-dinitrophenylhydrazono)-3-oxo-4,4-demethylvaleronitrile, relanium, melipramine, and other diverse chemical entities including unsaturated fatty acids (up to C₁₄ optimum), sulflaramid and its metabolite perfluorooctane sulfonamide (DESFA), perfluorooctanoate, clofibrate, Wy-14, 643, ciprofibrate,

and fluoroalcohols; ionophorous antibiotic uncouplers, including gramicidin, nigericin, tyrothricin, tyrocidin, valinomycin, alamethicins, harzianin HA V, saturnisporin SA IV, zervamicins, magainin, cecropins, melittin, hypelcins, suzukacillins, monensins, trichotoxins, antiameobins, crystal violet, cyanine dyes, cadmium ion, trichosporin-B and their derivatives; and other heterogeneous uncoupling compounds, including desaspidin, ionized calcium (Ca^{++}), uncoupling proteins such as UCPI-1, UCP-2, UCP-3, PUMP (Plant Uncoupling Mitochondrial Protein), histones, polylysines, A206668-a protein, and compound K23187.

46. The method of claim 37, wherein a second therapeutic agent or therapy is administered.

47. The method of claim 46, wherein the second therapeutic agent or therapy is selected from the group consisting of: anti-fungal agents, including Amphotericin B, Griseofulvin, Fluconazole (Diflucan), Intraconazole, 5 fluoro-cytosine (Flutocytosine, 5-FC), Ketatoconazole and Miconazole; anti-bacterial agents, including beta lactam rings (penicillins), macrocyclic lactone rings (macrolides), polycyclic derivatives of naphacenecarboxamide (tetracyclines), amino sugars in glycosidic linkages (aminoglycosides), peptides (bacitracin, gramicidin, polymyxins, etc.), nitrobenzene derivatives of dichloroacetic acid, large ring compounds with conjugated double bond systems (polyenes), various sulfa drugs including those derived from sulfanilamide (sulfonamides, 5-nitro-2-furyl compounds (nitrofurans), quinolone carboxylic acids (nalidixic acid), fluorinated quinolones (ciprofloxan, enoxacin, ofloxacin, etc.), nitroimidazoles (metronidazole), peptide antibiotics (such as bacitracin, bleomycin, cactinomycin, capreomycin, colistin, dactinomycin, gramicidin A, enduracitin, amphomycin, gramicidin J, mikamycins, polymyxins, stendomycin, actinomycin; aminoglycosides represented by streptomycin, neomycin, paromycin, gentamycin, ribostamycin, tobramycin, amikacin; lividomycin, beta lactams represented by benzylpenicillin, methicillin, oxacillin, hetacillin, piperacillin, amoxicillin and carbenicillin; lincosaminides represented by clindamycin, lincomycin, celesticetin, desalicyetin; chloramphenicol; macrolides represented by erythromycins, lankamycin, leucomycin, picromycin), nucleosides (such as 5-azacytidine, puromycin, septacidin and amicitin; phenazines represented by myxin, lomofungin, iodine), oligosaccharides (including curamycin and everminomycin; sulfonamides represented by sulfathiazole, sulfadiazine, sulfanilimide, sulfapyrazine) polyenes (including amphotericins, candicidin and nystatin, polyethers, tetracyclines (including doxycyclines, minocyclines, methacyclines, chlortetracyclines, oxytetracyclines, demeclocyclines), nitrofurans (including nitrofurazone, furazolidone, nitrofurantoin, furium, nitrovin and nifuroxime), and quinolone carboxylic acids

(including nalidixic acid, piromidic acid, pipemidic acid and oxolinic acid); antiviral agents including interferons α , β and γ , amantadine, rimantadine, arildone, ribavirin, acyclovir, abacavir, vidarabine (ARA-A) 9-1,3-dihydroxy-2-propoxy methylguanine (DHPG), ganciclovir, enviroxime, foscarnet, amplitgen, podophyllotoxin, 2,3-dideoxythymidine (ddC), iododeoxyuridine (IDU), trifluorothymidine (TFT), dideoxyinosine (ddi), d4T, 3TC, zidovudine, efavirenz, protease inhibitors such as indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, and specific antiviral antibodies; anti-cancer drugs, including cell cycle-specific agents (including structural analogs or antimetabolites of methotrexate, mercaptopurine, fluorouracil, cytarabine, thioguanine, azacitidine), bleomycin peptide antibiotics, such as podophyllin alkaloids including etoposide (VP-16) and teniposide (VM-26), various plant alkaloids such as vincristine, vinblastine, and paclitaxel, anti-neoplastic cell cycle-nonspecific agents such as various alkylating compounds such as busulfan, cyclophosphamide, mechlorethamine, melphalan, altaretamine, ifosfamide, cisplatin, dacarbazine, procarbazine, lomustine, carmustine, lomustine, semustine, chlorambucil, thiotepa and carboplatin; various hormones, hormone agonists and biologic response modifying agents, including flutamide, prednisone, ethinyl estradiol, diethylstilbestrol, hydroxyprogesterone caproate, medroxyprogesterone, megestrolacetate, testosterone, fluoxymesterone and thyroid hormones such as di-, tri- and tetraiodothyroidine, the aromatase inhibitor, amino glutethimide, the peptide hormone inhibitor octreotide and gonadotropin-releasing hormone agonists such as goserilin acetate and leuprolide, biologic response modifiers such as various cytokines, interferon alpha-2a, interferon alpha-2b, interferon-gamma, interferon-beta, interleukin-1, interleukin-2, interleukin-4, interleukin-10, monoclonal antibodies (anti-HER-2/*neu* humanized antibody), tumor necrosis factor, granulocyte-macrophage colony-stimulating factor, macrophage-colony-stimulating factor, various prostaglandins, phenylacetates, retinoic acids, leukotrienes, thromboxanes and other fatty acid derivatives; and radiation therapy.

48. A method of inducing heat shock proteins in an animal comprising the step of administering amount of a mitochondrial uncoupling agent sufficient to induce heat shock proteins.

49. The method of claim 48, wherein the mitochondrial uncoupling agent is 2,4 dinitrophenol.

50. The method of claim 48, wherein the mitochondrial uncoupling agent is selected from the group consisting of: classic uncouplers, including 2,4 dinitrophenol, clofazimine, albendazole, cambendazole, oxibendazole, triclabendazole (TCZ), 6-chloro-5-[2,3-dichlorophenoxy]-2-methylthio-benzimidazole and their sulfoxide and sulfone metabolites, thiobendazole, rafoxanide, bithionol, niclosamide, eutypine, various lichen acids (hydroxybenzoic acids) such as (+)usnic acid, vulpinic acid and atranorin, 2', 5-dichloro-3-t-butyl-4'-nitrosalicylanilide (S-13), 3, 4', 5-trichlorosalicylanilide (DCC), platanetin, 2-trifluoromethyl-4, 5, 6, 7- tetrachlorobenzimidazole (TTFB), 1799, AU-1421, 3,4,5,6,9,10-hexahydro-14,16-dihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1,7(8H)-dione (zearalenone), N,N¹-bis-(4-trifluoromethylphenyl)-urea, resorcylic acid lactones and their derivatives, 3,5-di-t-butyl-hydroxybenzylidenemalononitrile(SF6847), 2,2,-bis(hexafluoroacetyl) acetone, triphenyl boron, carbonylcyanide 4-trifluoromethoxyphenylhydrazone (FCCP), tributylamine (TBA), carbonyl cyanide 3-chlorophenylhydrazone (CICCP), 1, 3, 6, 8-tetranitrocarbazole, tetrachlorobenzotriazole, 4-iso-octyl-2,6-dinitrophenol(Octyl-DNP), 4-hydroxy-3,5-diidobenzonitrile, mitoguazone (methylglyoxal bisguanylhydrazone), pentachlorophenol (PCP), 5-chloro-2-mercatobenzothiazole (BZT-SH), tribromoimidazole (TBI), N-(3-trifluoromethylphenyl)-anthranilic acid (Flufenamic acid), 4-nitrophenol, 4, 6-dinitrocresol, 4-isobutyl-2,6-dinitrophenol, 2-azido-4-nitrophenol, 5-nitrobenzotriazole, 5-chloro-4-nitrobenzotriazole, tetrachlorobenzotriazole, methyl-o-phenylhydrazone, N-phenylanthranilic acid, N-(3-nitrophenyl)anthranilic acid, N-(2,3-dimethylphenyl) anthranilic acid, mefenamic acid, diflunisal, flufenamix acid, N-(3-chlorophenyl) anthranilic acid, carbonyl cyanide 4-trifluoromethoxyphenylhydrazone (FCCP), SR-4233 (Tirapazamine), atovaquone, carbonyl cyanide 4-(6'-methyl-2'-benzothiazyl)-phenylhydrazone(BT-CCP), ellipticine, olivacine, ellipticinium, isoellipticine and related isomers, methyl-0-phenylhydrazonocynoacetic acid, methyl-0-(3-chlorophenylhydrazono) cyanoacetic acid, 2-(3'-chlorophenylhydrazono)-3-oxobutyronitrile, thiosalicylic acid, 2-(2',4-dinitrophenylhydrazono)-3-oxo-4,4-demethylvaleronitrile, relanium, melipramine, and other diverse chemical entities including unsaturated fatty acids (up to C₁₄ optimum), sulflaramid and its metabolite perfluorooctane sulfonamide (DESFA), perfluorooctanoate, clofibrate, Wy-14, 643, ciprofibrate, and fluoroalcohols; ionophorous antibiotic uncouplers, including gramicidin, nigericin, tyrothricin, tyrocidin, valinomycin, alamethicins, harzianin HA V, saturnisporin SA IV, zervamicins, magainin, cecropins, melittin, hypelcins, suzukacillins, monensins, trichotoxins, antiameobins, crystal violet, cyanine dyes, cadmium ion, trichosporin-B and their derivatives;

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and other heterogeneous uncoupling compounds, including desaspidin, ionized calcium (Ca^{++}), uncoupling proteins such as UCPI-1, UCP-2, UCP-3, PUMP (Plant Uncoupling Mitochondrial Protein), histones, polylysines, A206668-a protein, and compound K23187.

- 5 51. The method of claim 48, wherein the mitochondrial uncoupling agent is a conjugate comprising 2,4 dinitrophenol.
52. The method of claim 48, further wherein the induced heat shock proteins condition the animal for a specific condition.
- 10 53. The method of claim 52, wherein the specific condition is surgery.
54. The methods of claims 1, 15, 29, 48 and 51, wherein the uncoupling agent is produced using combinatorial technology.